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Research Paper

The limits of single-group interrupted time series analysis in assessing the impact of smoke-free laws on short-term mortality

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ABSTRACT

Background: Decreases in circulatory/respiratory morbimortality after the January-2006 Spanish partial smoke-free law have been found using designs without control groups, such as single-group interrupted time series (ITS), which are prone to biases. The aim was to reassess the law's impact on mortality using ITS designs with robustness checks.
Methods: A comprehensive cohort of people aged ≥25 in each calendar-year of 2002–2007, living in 13 of 18 Spanish regions, was followed up between 01/2002 and 12/2007. The law included a smoking ban in indoor public and workplaces, allowing exceptions in catering, hospitality and leisure venues, and other interventions. Post-law changes in monthly coronary/respiratory mortality were estimated using segmented regression, adjusting for relevant covariates, including seasonality, extreme temperatures, influenza incidence and air pollution. The validity of results was assessed using control outcomes, hypothetical law dates, and non-equivalent control groups, analysing their results as difference-in-differences (DID) designs.
Results: Significant immediate post-law decreases in coronary, respiratory and non-tobacco-related mortality were observed among people aged ≥70. A significant immediate post-law decrease in respiratory mortality (−12.7%) was also observed among people age 25–69, although this was neutralized by a subsequent upward trend before 1.5 years. More favourable post-law changes in coronary/respiratory mortality among the target (people aged 25–69) than control groups (people aged ≥70 or women aged ≥80) were not identified in DID designs. Establishing hypothetical law dates, immediate decreases began in February/March 2005 with maxima between April and July 2005.
Conclusions: After robustness checks, the results do not support a clear positive impact of the 2006 Spanish smoke-free law on short-term coronary/respiratory mortality. The favourable immediate changes observed pre- and post-law could derive mainly from the harvesting effect of the January-2005 cold wave. This highlights the risks of assessing the impact of health interventions using both morbimortality outcomes and designs without a control group and adequate robustness checks.

Introduction

Interrupted time series (ITS) are valuable quasi-experimental designs to assess the impact of public health interventions (i.e., smoke-free laws) (Craig et al., 2012). The most basic design, widely used when a comparable control group is not available (i.e., large-scale interventions targeting the entire population), is sometimes named single-group ITS (Linden, 2017).

Data are often analysed using segmented regression models, which allow us to characterize changes in outcomes (i.e., mortality), measured regularly over time, and identify possible explanatory factors. The time series is broken into segments (typically two, pre- and post-intervention), each of which can exhibit both a level and a trend. The level is the outcome value at the beginning of each segment (i.e., the y-intercept or its value immediately following the change-point). The trend is the rate of change in outcome during a segment (Lopez-Bernal, Cummins, &

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Gasparrini, 2017; Wagner, Soumerai, Zhang, & Ross-Degnan, 2002). The key assumption is that without intervention (counterfactual), the level and trend in outcome would remain unchanged throughout the study period provided that other factors affecting the outcome remain unchanged or change slowly (Linden, 2017).

Single-group ITS designs have important strengths, among them: a) They allow adjustment for pre-intervention underlying trends (which would imply some control for unmeasured time-varying confounders (Barone-Adesi, Gasparrini, Vizzini, Merletti, & Richiardi, 2011; Seguret, Ferreira, Cambou, Carriere, & Thomas, 2014) and for measured ecological confounding factors such as seasonality, climate indicators or other interventions sufficiently separated in time. b) They are quick and cheap to implement because they use data routinely collected for administrative purposes (Penfold & Zhang, 2013). However, they are prone to important internal validity threats (Linden, 2017; Salway, Sims, & Gilmore, 2014), and they remain vastly inferior to designs with a comparable control group as counterfactual (Linden, 2017). The main threats are unplanned events or exposures close in time to the intervention that could influence the outcome, which are often very difficult to identify or control in the absence of non-intervention groups, usually resulting in overestimation of the intervention's effect. Morbimortality outcomes are especially threatened by representing the end of the causal chains (Gasparrini, Gorini, & Barchielli, 2009; Linden, 2017).

Smoke-free laws can have a significant impact on population mortality through reductions in exposure to second-hand tobacco smoke and smoking prevalence. Although the greatest benefit will probably be in the long term, there may also be favourable effects on short-term circulatory/respiratory mortality because even brief second-hand smoke exposures lead to rapid alterations in coronary vessels, coagulation mechanisms, lung function and airway inflammatory response that can cause acute coronary events, acute respiratory symptoms and worsening of respiratory diseases (Flouris & Koutedakis, 2011; UDHHS, 2014)

However, circulatory/respiratory mortality after a smoke-free law may also be influenced by multiple ecological factors or concurrent events that modify either the prevalence or intensity of smoking (tobacco price, economic cycle, other preventive interventions, smoking cessation treatments, etc.) or the occurrence or prognosis of tobacco-related health problems (ambient temperature, air pollution, flu incidence, health care, etc.). In addition, immediate favourable post-law changes could be compensations for short-term excess mortality occurring months before the intervention (harvesting) due to previous cold waves, for example. To assess the validity of results for causal inference, some robustness checks have been proposed, such as using non-equivalent control groups and control outcomes that are predicted not to change or change less than target ones due to the intervention, as well as testing for false intervention dates (Linden, 2015). The internal validity may be challenged if larger favourable changes in outcome are found for control groups, control outcomes or false intervention dates (Linden, 2017).

Unfortunately, most previous studies assessing smoking ban effectiveness through single-group ITS have focused exclusively on circulatory (usually coronary) or respiratory morbimortality, omitting all or some robustness checks. Furthermore, although confounders such as seasonality, influenza incidence, environmental temperature or air pollution have sometimes been controlled (Frazer, McHugh, Callinan, & Kelleher, 2016), others, like the economic cycle or harvesting, are rarely considered. Thus, premature conclusions on the impact of smoke-free laws are likely to be established.

Based on designs without control groups and robustness checks, a temporal relationship between implementation of the 2006 Spanish partial smoke-free law (which allowed wide exceptions in catering and hospitality sectors) and subsequent reductions in circulatory or respiratory morbimortality has been suggested (Aguero et al., 2013; Galan et al., 2015, 2017; Villalbi et al., 2009, 2011). It is rather strange that the authors were not surprised to find the greatest relative favourable impact in the elderly, when it would be expected to be found in working-age people, since the law was especially targeted at workplaces; furthermore, the highest prevalence of smoking and second-hand smoke exposure is usually found in the latter group (Meyers, Neuberger, & He, 2009; Twose, Schiaffino, Garcia, Borras, & Fernandez, 2007; Zeng et al., 2016).

The study objective was to reassess the impact of the 2006 Spanish partial smoke-free law on short-term coronary or respiratory mortality using ITS designs with robustness checks in the framework of a comprehensive cohort.

Methods

Study population

A cohort was drawn from the 2001 Census, including all residents in Spain on November 1, 2001. 40,847,371 individuals were followed up by the National Statistics Institute (INE) until December 31, 2011 to determine vital status and cause of death. The INE retrospectively performed the record linkage between census and population and mortality registers using personal identifiers, providing researchers with an anonymized data file, including sociodemographic characteristics at baseline (census date) and health outcomes (vital status, calendar-month, region and cause of death) during the follow-up period. Census participants not found in population or mortality registers were excluded (1.7%), and risk contribution of participants having moved abroad was censored (< 1%). The sociodemographic characteristics of excluded or censored participants did not differ from included participants.

This study included the 21,189,941 people alive at baseline in 13 of Spain's 18 regions and aged ≥25 in each calendar-year of the 2002–2007 period (73.5% of the total Spanish population aged ≥25); in the remaining five regions, air pollution indicators were not available. The INE Institutional Review Board approved the study. Ethics Committee approval was not required as the database included no personal identifiers.

Measurements

The target outcomes for which a greater favourable impact of the law was expected considering the physiopathology of tobacco smoke exposure (Jayes et al., 2016; Lv et al., 2015; UDHHS, 2010) were coronary mortality (ICD-10: I20-I25) and respiratory mortality (ICD-10: J00-J99), while the control outcome was mortality from non-tobacco-related diseases, including diseases other than cancer, circulatory, respiratory and infectious/parasitic diseases (ICD-10: D50-D89, K00-Q99, R00-R74, R76-R99). The 2006 partial Spanish smoke-free law came into force on January 1, 2006, including a smoking ban in indoor public places and workplaces, allowing wide exceptions in catering, hospitality, party and gambling venues, a complete ban on tobacco advertising, promotion and sponsorship, and a reduction in tobacco sales outlets. We considered as covariates: sequential calendar-month, month of the year (seasonality), region of residence at baseline, gender, age as time-varying, and aggregate indicators at regional and monthly level such as influenza incidence rate, heat-wave days, cold-wave days, ventile of minimum and maximum temperatures, and air concentration of nitrogen dioxide (NO_2) and particles < 10 µm in diameter (PM10). Supplementary Table S1 shows details on the law and included variables.

Statistical analysis

Directly age-standardized mortality rates by calendar-year were calculated using weights from the 2013 European Standard Population. To assess the law's possible impact on mortality, the monthly mortality rates (outcome) were modelled using log-linked negative binomial

Table 1
Directly Age-Standardized Mortality Rate from Coronary, Respiratory and Non-Tobacco-Related Diseases by Calendar-year of Death in a Spanish Cohort.

	People aged 25–69			People aged ≥70			Women aged ≥80		
	Rate	95%CI		Rate	95%CI		Rate	95%CI	
Calendar-year	Coronary heart diseases								
2002	37	36	38	609	600	617	971	948	993
2003	38	37	39	619	611	628	981	959	1003
2004	35	34	35	595	587	603	957	935	978
2005	34	33	35	587	579	595	936	915	956
2006	32	31	33	531	524	539	860	840	879
2007	32	31	33	512	505	519	822	803	840
2002–2005	36	35	36	602	598	606	960	949	971
2006–2007	32	31	33	521	516	527	840	827	854
Change in mortality rate between periods (%)	−11.1	−13.2	−9.0	−13.4	−14.5	−12.4	−12.5	−14.2	−10.8
	Respiratory diseases								
2002	21	21	22	723	714	732	1044	1020	1067
2003	21	20	22	762	753	771	1145	1121	1169
2004	18	18	19	674	666	683	992	970	1014
2005	21	20	22	797	788	807	1225	1201	1249
2006	18	17	19	638	629	646	965	944	986
2007	20	19	20	673	664	681	1008	987	1029
2002–2005	21	20	21	740	735	744	1103	1092	1115
2006–2007	19	18	19	655	649	661	987	972	1002
Change in mortality rate between periods (%)	−8.3	−11.1	−5.4	−11.4	−12.4	−10.5	−10.5	−14.2	−10.8
	Non-tobacco-related diseases								
2002	56	55	58	1280	1267	1292	2579	2543	2616
2003	58	56	59	1362	1350	1375	2794	2757	2831
2004	55	54	56	1305	1293	1317	2666	2630	2702
2005	56	54	57	1352	1340	1364	2814	2778	2850
2006	54	53	55	1256	1245	1268	2590	2556	2623
2007	56	54	57	1238	1227	1249	2547	2514	2579
2002–2005	56	56	57	1326	1320	1332	2716	2698	2734
2006–2007	55	54	56	1247	1239	1255	2568	2544	2591
Change in mortality rate between periods (%)	−2.3	−4.1	−0.6	−5.9	−6.7	−5.2	−5.5	−6.5	−4.4

Rate: Directly age-standardized mortality rate per 100,000 person-years using the weights of the 2013 European Standard Population. **95%CI**: Confidence interval at 95%. **Change in mortality rate between periods (%)**: Percent change in age-standardized mortality rate between 2002–2005 (pre-law period) and 2006–2007 (post-law period). **Non-tobacco-related diseases**: Non-traumatic causes other than circulatory, respiratory, cancer and infectious/parasitic diseases.

regression models in the framework of generalized linear models. In these models the log of person-months at risk is included as an offset variable. We first built models including calendar-year as a categorical variable of interest and age, region of residence, seasonality, influenza, heat and cold wave days, and air concentration of PM10 and NO_2 as adjustment variables. Subsequently, we fit segmented regression models (Lopez-Bernal et al., 2017; Wagner et al., 2002), which can be formalized as: $Y_t = \beta_0 + \beta_1 T_t + \beta_2 X_t + \beta_3 X_t T_t + \beta_k X_k + \varepsilon$, where Y_t is the log of monthly mortality rates measured at each calendar-month of observation t, T_t is a continuous variable whose value for each calendar-month was the number of months elapsed since January 2002 (1–72), X_t a binary predictor for the law with a value of zero in the pre-law (January 2002–December 2005) and 1 in the post-law period (January 2006–December 2007), and $X_t T_t$ is an interaction term of law with time. In this model β_0 represents the intercept or baseline mortality level, β_1 the change in outcome for each unit increase in sequential calendar-month (underlying pre-intervention trend), β_2 and β_3 the immediate level change and the slope or trend change in outcome following the intervention, respectively, and β_k the coefficients of different covariates. To facilitate the interpretation, we transformed the β regression coefficients to percent changes (PC) as 100 (e^{β}–1), which were expressed as annual percent changes (APC) for trends. Changes were considered favourable if PC was negative and statistically significant ($P < 0.05$). The 95% confidence interval (95%CI) of PC was estimated as 100 ($e^{\beta \pm 1.96SE}$–1), where SE is the standard error of β.

The validity of results was assessed using three strategies: a) Comparing the post-law changes in mortality between a target or intervention group (people aged 25–69) and a non-equivalent control group (alternatively people aged ≥70 or women aged ≥80) in a kind of difference in differences (DID) design. People aged 25–69 were considered the target group because working-age people are much more exposed to second-hand smoke in workplaces (where the law was especially targeted) and leisure facilities than older people (Gasparrini et al., 2009; Twose et al., 2007). First, the groups were compared based on age-standardized mortality rates and later using multiple-group ITS regression models. These models can be formalized as: $Y_t = \beta_0 + \beta_1 T_t + \beta_2 X_t + \beta_3 X_t T_t + \beta_4 Z + \beta_5 Z T_t + \beta_6 Z X_t + \beta_7 Z X_t T_t + \beta_k X_k + \varepsilon$, where Z is a binary variable defining the intervention (Z = 1) or control (Z = 0) group, and ZT_t, ZX_t, and ZX_tT_t are additional interaction terms. β_0 to β_3 represent the control group and β_4 to β_7 the target group. Specifically, β_7 represents the difference in the post-law change in slope between the target and control group (DID of slopes) (Linden, 2019). A negative and statistically significant DID is interpreted as a more favourable or less unfavourable change in the target than control group, which, if there were no important differences in the pre-law trend, would allow attribution of changes to the smoke-free law (Angrist & Pischke, 2009). b) Comparing post-law changes in coronary and respiratory mortality considered as target outcomes with changes in mortality from non-tobacco related diseases considered as control outcome. c) Estimating the immediate level changes at false dates of law implementation both before and after the true date.

No relevant first-order linear autocorrelation was found using the Durbin-Watson statistic (DW). Thus, the DW range was 1.89–1.99 in models for different age groups and cause of death. Finally, various sensitivity analyses were performed by replacing in the standard segmented regression models the linear underlying trend for a quadratic one, or the heat- and cold-wave days by the ventile of maximum and minimum temperatures, or by removing the air pollution indicators (which allowed analysis for all of Spain with 28,716,744 people at risk).

Analyses were performed using Stata V.14.0 (Stata Corporation, College Station, Texas, USA).

Results

General characteristics

The monthly averages of influenza incidence, heat- and cold-wave days, and PM10 were significantly higher in the pre- than post-law period. The maximum heat-, cold-wave days and influenza incidence appeared in 2003, 2005 and 2003, respectively. There were more heat-wave days in 2003 than other years (mean 1.6 vs. < 0.9 days/month), and more cold-wave days in 2005 (mean 1.4 vs. < 0.7 days/month) (Table S2). The 2003 heat wave was concentrated in August (10.6 days) and the 2005 cold wave in January (4.5 days). Maximum influenza incidence occurred in January 2005 with 2144 cases/100,000 inhabitants (data not shown).

Changes in age-standardized mortality rates

The age-standardized mortality rates by calendar-year and calendar-month are shown in Tables 1 and S3–S5, respectively. The highest rates were found in 2003 for coronary and non-tobacco-related mortality and in 2005 for respiratory mortality. Mortality rates from coronary, respiratory and non-tobacco related diseases were lower ($P < 0.05$) in the post-law (2006–2007) than pre-law period (2002–2005), both in the target (people aged 25–69) and control groups (people aged ≥70 or women aged ≥80); the percent decreases in mortality rates between periods were always of similar or greater magnitude in the control than the target group (Table 1). This can be easily observed when plotting the rates on a logarithmic scale (Fig. 1). Thus, the difference in post-law percent decrease between people aged 25–69 and ≥70 in mortality rates from coronary, respiratory and non-tobacco related diseases was 2.3% (95%CI: −0.2 to 4.7), 3.2% (95%CI: 0.2–6.2) and 3.6% (95%CI: 1.7–5.5), respectively, whereas the corresponding differences between people aged 25–69 and women aged ≥80 were 1.4% (95%CI: −1.3 to 4.1), 2.3% (95%CI: −1.0 to 5.5) and 3.1% (95%CI: 1.0–5.2), respectively.

Mortality risk by calendar-year

Results from models using calendar-year of death as a proxy for law implementation and adjusting for age, gender, region of residence, seasonality, influenza incidence, cold- and heat-wave days, PM10 and NO_2 are shown in Table 2. Coronary, respiratory and non-tobacco-related mortality were significantly lower in the post-law than pre-law period among people aged 25–69 and ≥70. The decreases were more intense for coronary and respiratory mortality than non-tobacco-related mortality. Peaks in mortality appeared in 2003 (especially coronary and non-tobacco-related mortality) and 2005 (especially respiratory mortality), which were often followed by significant declines the following year, especially among people aged ≥70.

Changes in mortality risk after implementation of partial smoke-free law

Focusing on impact models specifying both level and trend changes, statistically significant level decreases were observed immediately after law implementation in respiratory mortality among people aged 25–69 and in coronary, respiratory and non-tobacco-related mortality among people aged ≥70. However, the immediate decreases in respiratory mortality were followed by intense upward trends during the two years following the law among both people aged 25–69 and those ≥70. The decline among people aged 25–69 (−12.7%) was neutralized before 1.5 years, due to an 8.6% annual increase during the two years after law implementation. The same occurred with non-tobacco-related mortality among people aged 25–69 (Table 3).

Using difference in differences regression models with people aged 25–69 as the target group and people aged ≥70 as the control group, we did not identify more favourable or less unfavourable post-law changes in coronary or respiratory mortality among the target than control groups. In fact, the DID of slopes between target and control group for coronary, respiratory and non-tobacco related mortality were 2.7% (95% CI: −2.0 to 7.5), 2.6% (95% CI: −3.4 to 8.6) and 7.4% (95% CI: 3.8–11.1), respectively. The results were similar taking women aged ≥80 as the control group.

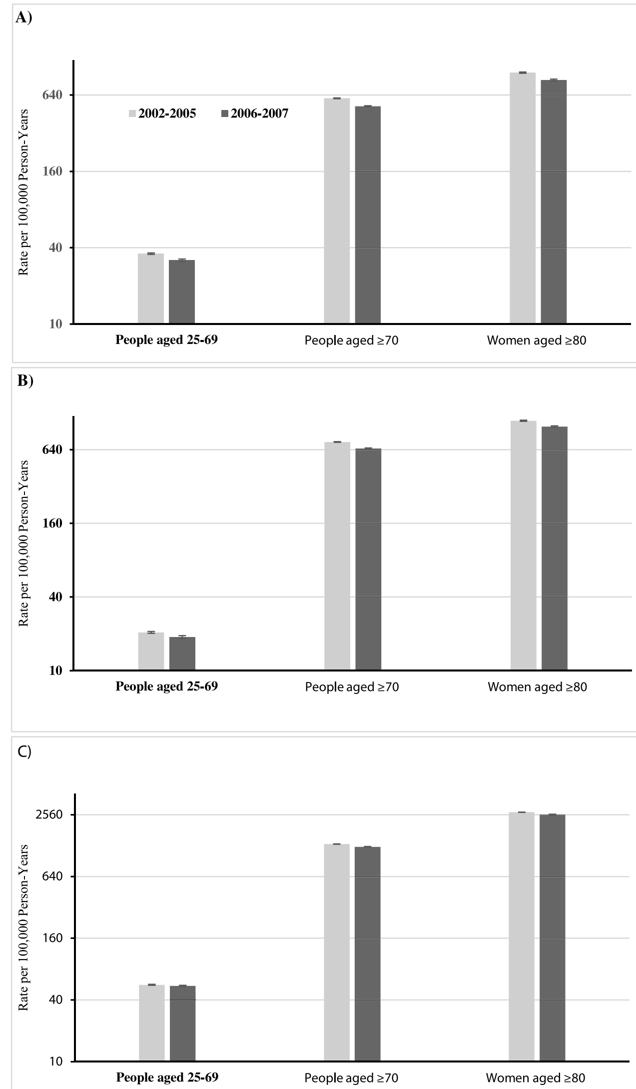

Fig. 1. Age-standardized mortality rate from coronary, respiratory and non-tobacco related disease among people aged 25–69, people aged ≥70 and women age ≥80 before (2002–05) and after (2006–07) implementation of smoke-free law.
A) Coronary disease; B) Respiratory disease; C) Non-tobacco-related disease.

Changes in mortality risk after introducing hypothetical law dates

Immediate decreases in coronary, respiratory and non-tobacco-related mortality were observed several months before the true date of law implementation. Such decreases were greater among people aged ≥70, occurring between February/March 2005 and the end of 2006, reaching maximum intensity between April and July 2005. Decreases among people aged 25–69 began and reached maximum intensity on similar dates, but lasted only until early 2006 (respiratory and non-tobacco-related mortality) or ceased to be relevant before the true implementation date (coronary mortality). Decreases in respiratory mortality were very similar between the maximum (July 2005) and true implementation date (Table 4). The difference-in-differences regression

Table 2
Adjusted Mortality Rate Ratio from Coronary, Respiratory and Non-Tobacco-Related Diseases by Calendar-Year of Death in a Spanish Cohort.

	People aged 25–69			People aged ≥70			Women aged ≥80		
	RR	95%CI		RR	95%CI		RR	95%CI	
Calendar-year	Coronary heart diseases								
2002	1.00	.	.	1.00	.	.	1.00	.	.
2003	1.01	0.97	1.06	0.98	0.96	1.01	0.96	0.93	1.00
2004	0.92	0.88	0.97	0.96	0.94	0.99	0.97	0.93	1.00
2005	0.90	0.86	0.94	0.93	0.90	0.95	0.92	0.89	0.97
2006	0.86	0.82	0.90	0.85	0.83	0.87	0.86	0.83	0.90
2007	0.85	0.81	0.88	0.82	0.80	0.84	0.83	0.79	0.86
2002–2005	1.00	.	.	1.00	.	.	1.00	.	.
2006–2007	0.89	0.87	0.92	0.86	0.85	0.88	0.88	0.86	0.90
	Respiratory diseases								
2002	1.00	.	.	1.00	.	.	1.00	.	.
2003	1.00	0.94	1.06	1.03	1.01	1.06	1.08	1.04	1.13
2004	0.90	0.85	0.96	0.97	0.94	0.99	1.02	0.98	1.07
2005	1.03	0.97	1.10	1.08	1.05	1.10	1.19	1.14	1.25
2006	0.90	0.85	0.96	0.89	0.87	0.91	0.98	0.93	1.02
2007	0.96	0.90	1.01	0.93	0.90	0.95	1.00	0.96	1.05
2002–2005	1.00	.	.	1.00	.	.	1.00	.	.
2006–2007	0.95	0.91	0.98	0.89	0.88	0.90	0.92	0.90	0.94
	Non-tobacco-related diseases								
2002	1.00	.	.	1.00	.	.	1.00	.	.
2003	1.01	0.97	1.04	1.03	1.01	1.05	1.05	1.02	1.08
2004	0.97	0.94	1.01	1.01	0.99	1.03	1.03	1.00	1.07
2005	0.97	0.94	1.01	1.02	1.00	1.04	1.07	1.03	1.10
2006	0.95	0.92	0.99	0.96	0.94	0.98	0.99	0.96	1.02
2007	0.98	0.95	1.02	0.95	0.93	0.97	0.97	0.94	1.00
2002–2005	1.00	.	.	1.00	.	.	1.00	.	.
2006–2007	0.98	0.96	1.00	0.96	0.95	0.97	0.94	0.93	0.96

RR: Mortality rate ratio adjusted by region of residence, age at death, seasonality, influenza incidence, nº of extremely cold days, nº of extremely hot days, and air concentration of PM10 and NO_2 using negative binomial regression with log link. 95%CI: Confidence interval at 95%. Non-tobacco-related diseases: Non-traumatic causes other than circulatory, respiratory, cancer and infectious/parasitic diseases.

models for a law implementation date six months prior to the true date (July 2005 versus January 2006) did not identify more favourable or less unfavourable post-law changes in coronary or respiratory mortality in the target than the control groups.

Discussion

Main findings

Results from a natural experiment in which national cohort data were analysed using an ITS design, includingcareful adjustment for relevant covariates and performing robustness checks, did not support a clear favourable impact of the 2006 Spanish partial smoke-free law on short-term coronary/respiratory mortality. Thus, although significant immediate post-law decreases in coronary (people aged ≥70) and respiratory mortality (people aged ≥25) were observed, there were also significant decreases in non-tobacco related mortality among people aged ≥70, and the decreases among people age 25–69 were neutralized before 1.5 years by a subsequent upward trend. Moreover, we did not identify more favourable post-law changes in coronary/respiratory mortality among the target group (people aged 25–69) than the control groups (people aged ≥70 or women aged ≥80). Finally, when we

Table 3
Level and Trend Changes in Mortality Risk from Coronary, Respiratory and Non-Tobacco-Related Diseases after Implementation of a Partial Smoke-Free Law in a Spanish Cohort, 2002–2007.

	Pre-law linear trend			Level change			Linear trend change		
	APC	95%CI		PC	95%CI		APC diff	95%CI	
Coronary heart diseases									
People aged 25–69	−4.0	−5.4	−2.6	−1.3	−6.6	4.2	2.1	−2.0	6.3
People aged ≥70	−2.6	−3.4	−1.8	−5.8	−8.5	−3.0	−1.0	−3.1	1.1
Women aged ≥80	−2.4	−3.6	−1.1	−4.4	−8.7	0.2	−1.6	−4.8	1.7
Respiratory diseases									
People aged 25–69	−0.1	−2.1	1.9	−12.7	−19.0	−6.0	8.6	3.0	14.6
People aged ≥70	1.3	0.5	2.2	−18.3	−20.7	−15.8	4.9	2.7	7.1
Women aged ≥80	4.3	2.8	5.8	−20.5	−24.5	−16.4	2.2	−1.4	5.8
Non-tobacco-related diseases									
People aged 25–69	−1.2	−2.4	−0.1	−3.1	−7.2	1.2	4.5	1.3	7.8
People aged ≥70	0.4	−0.2	1.0	−5.8	−7.9	−3.7	−1.5	−3.1	0.0
Women aged ≥80	1.7	0.7	2.7	−7.2	−10.4	−3.8	−3.0	−5.4	−0.6

Negative binomial regression model specifying terms for both level and linear trend changes after law implementation. Results are adjusted by underlying linear trend, region of residence, age at death, seasonality, influenza incidence, nº of extremely cold days, nº of extremely hot days, and air concentration of PM10 and NO_2. APC: Annual percent change; PC: Percent change; APC diff: Difference in APC between pre-law and post-law periods. 95%CI: Confidence interval at 95%. Non-tobacco-related diseases: Non-traumatic causes other than circulatory, respiratory, cancer and infectious/parasitic diseases.

Table 4
Level Changes in Mortality Risk from Coronary, Respiratory and Non-tobacco-Related Diseases after Hypothetical Dates of Implementation of a Partial Smoke-Free Law in a Spanish Cohort, 2002–2007.

	Coronary heart diseases						Respiratory diseases						Non-tobacco-related diseases					
	People aged 25–69			People aged ≥70			People aged 25–69			People aged ≥70			People aged 25–69			People aged ≥70		
Date	PC	95%CI		PC	95%CI		PC	95%CI		PC	95%CI		PC	95%CI		PC	95%CI	
01/01/2005	−1.1	−6.0	3.9	−0.7	−3.3	2.0	13.0	5.5	21.0	9.8	6.8	12.9	−1.4	−5.3	2.6	1.0	−1.2	3.1
01/02/2005	−4.0	−8.6	0.9	−7.1	−9.5	−4.6	0.4	−6.1	7.3	−5.8	−8.4	−3.1	−2.6	−6.3	1.4	−3.8	−5.8	−1.8
01/03/2005	−4.8	−9.3	0.0	−8.7	−11.0	−6.2	−3.1	−9.4	3.6	−12.2	−14.6	−9.8	−5.1	−8.8	−1.3	−5.9	−7.8	−3.9
01/04/2005	−4.6	−9.3	0.2	−10.6	−12.9	−8.1	−5.7	−12.0	0.9	−18.3	−20.5	−16.0	−6.8	−10.4	−3.0	−8.4	−10.3	−6.5
01/05/2005	−3.4	−8.1	1.5	−10.1	−12.4	−7.6	−8.4	−14.5	−1.9	−19.4	−21.6	−17.1	−4.8	−8.5	−0.9	−8.8	−10.7	−6.9
01/06/2005	−2.1	−6.9	2.9	−8.8	−11.2	−6.3	−11.6	−17.5	−5.3	−19.6	−21.8	−17.4	−4.7	−8.4	−0.8	−9.4	−11.2	−7.5
01/07/2005	−3.8	−8.5	1.2	−8.0	−10.5	−5.5	−13.2	−19.0	−7.0	−19.7	−21.9	−17.5	−5.5	−9.2	−1.7	−8.8	−10.7	−6.9
01/08/2005	−0.5	−8.3	8.0	−6.9	−9.4	−4.3	−11.7	−17.6	−5.3	−19.4	−21.6	−17.1	−4.7	−8.5	−0.8	−7.8	−9.7	−5.8
01/09/2005	−1.7	−6.5	3.4	−6.0	−8.6	−3.5	−11.1	−17.0	−4.7	−18.3	−20.5	−16.0	−4.0	−7.8	−0.1	−6.5	−8.4	−4.5
01/10/2005	−0.9	−5.8	4.3	−5.5	−8.0	−2.8	−10.4	−16.4	−3.9	−18.2	−20.4	−15.9	−4.3	−8.1	−0.4	−5.6	−7.6	−3.6
01/11/2005	−0.7	−5.6	4.5	−5.1	−7.7	−2.5	−10.9	−17.0	−4.5	−19.0	−21.3	−16.7	−3.7	−7.6	0.3	−5.8	−7.8	−3.8
01/12/2005	−0.4	−5.4	4.9	−6.5	−9.0	−3.9	−12.0	−18.0	−5.5	−18.4	−20.7	−16.1	−3.9	−7.8	0.2	−5.9	−7.9	−3.9
01/01/2006	**−1.3**	**−6.6**	**4.2**	**−5.8**	**−8.5**	**−3.0**	**−12.7**	**−19.0**	**−6.0**	**−18.3**	**−20.7**	**−15.8**	**−3.1**	**−7.2**	**1.2**	**−5.8**	**−7.9**	**−3.7**
01/02/2006	−1.1	−6.5	4.6	−2.9	−5.7	0.1	−7.0	−13.8	0.4	−11.5	−14.2	−8.8	−2.7	−6.9	1.7	−4.2	−6.3	−2.0
01/03/2006	−0.1	−5.6	5.8	−2.5	−5.4	0.5	−3.2	−10.4	4.6	−7.4	−10.2	−4.5	−1.1	−5.5	3.4	−4.4	−6.6	−2.2
01/04/2006	−3.5	−8.9	2.3	−4.8	−7.6	−1.9	−3.7	−10.9	4.2	−6.7	−9.6	−3.7	0.1	−4.3	4.7	−4.4	−6.5	−2.2
01/07/2006	−0.1	−5.9	6.2	−3.1	−6.1	−0.1	−0.9	−8.8	7.7	−5.2	−8.2	−2.0	−1.5	−6.1	3.2	−2.9	−5.2	−0.5
01/10/2006	−0.5	−6.7	6.0	−4.8	−7.8	−1.6	−2.8	−10.7	5.8	−6.7	−9.8	−3.4	1.2	−3.7	6.2	−7.0	−9.2	−4.6
01/01/2007	1.8	−5.5	9.7	−2.4	−6.1	1.5	0.2	−8.9	10.2	−2.9	−6.7	1.0	3.2	−2.6	9.5	−2.8	−5.6	0.2

The true date of law implementation was 01/01/2006 and its results have been marked in bold. The rest are hypothetical dates of law implementation.
A level- and trend-change impact model was specified, although only level changes are shown. Results are adjusted by underlying linear trend, region of residence, age at death, seasonality, influenza incidence, nº of extremely cold days, nº of extremely hot days, and air concentration of PM10 and NO_2.
PC: Percent change. 95%CI: Confidence interval at 95%. Non-tobacco-related diseases: Non-traumatic causes other than circulatory, respiratory, cancer and infectious/parasitic diseases.

established hypothetical law implementation dates, we found that the immediate decreases in mortality began in February/March 2005, with maxima between April and July 2005, several months before the true implementation date.

No support for causal attribution of changes in coronary/respiratory mortality to smoke-free law

After robustness checks, the results in no way support a causal attribution of the favourable changes in coronary/respiratory mortality observed before and immediately after January 2006 to implementation of the smoke-free law. A clear favourable impact of the law should be supported by relevant and sustained post-law decreases in coronary/respiratory mortality at age 25–69, since at these ages exposure to tobacco smoke in indoor workplaces (where the law is especially targeted) and leisure facilities is much greater than in older people (Meyers et al., 2009; Twose et al., 2007; Zeng et al., 2016). Moreover, the association between smoking and respiratory – and especially coronary problems – is stronger at younger than older ages (Barone-Adesi, Vizzini, Merletti, & Richiardi, 2006; Meyers et al., 2009; Tan & Glantz, 2012), and it seems that smoking bans encourage cessation particularly among young smokers (Fichtenberg & Glantz, 2002; Meyers et al., 2009). Thus, many studies elsewhere have found greater decreases in tobacco smoke exposure or risk of coronary events in younger than older people following smoking bans (Barone-Adesi et al., 2011; Cox, Vangronsveld, & Nawrot, 2014; Meyers et al., 2009; Sims, Maxwell, Bauld, & Gilmore, 2010; Tan & Glantz, 2012), although some studies have not reached a similar conclusion (Lee, Fry, & Forey, 2014; Nazzal & Harris, 2017; Sims et al., 2010). However, among people aged 25–69 a significant post-law decrease in coronary mortality was not observed, and the immediate decrease observed in respiratory mortality was neutralized before 1.5 years by a subsequent upward trend. Moreover, the difference-in-differences regression models did not identify more favourable or less unfavourable post-law changes in coronary/respiratory mortality among the target (people aged 15–69) than the control group (people aged ≥70 or women aged ≥80). It is particularly surprising that post-law decreases in coronary/respiratory mortality were also identified among women aged ≥80, a group that probably had very low tobacco smoke exposure in indoor workplaces and leisure facilities (Twose et al., 2007).

Harvesting as an explanation of changes in coronary/respiratory mortality

The favourable post-law changes in coronary, respiratory and non-tobacco-related mortality among people aged ≥70, which began 9–10 months before the law came into effect, are strongly suggestive of a harvesting phenomenon or mortality displacement caused by the January-2005 cold wave and flu epidemic. There is evidence that these events have increased adverse effects on short-term circulatory/respiratory mortality among the most fragile population, especially the elderly (Barone-Adesi et al., 2006; Bunker et al., 2016; Ryti, Guo, & Jaakkola, 2016), which would have precipitated their death, decreasing mortality in the following months (after February/March). It could be argued that the observed pre-law decreases may have resulted from implementation of smoking bans before the law came into force in certain indoor places, as reported elsewhere (Christensen, Moller, Jorgensen, & Pisinger, 2014; Juster et al., 2007; Sims et al., 2010). Unfortunately, there are no data on the law implementation process to rule out this hypothesis. It is possible that the smoking ban was implemented in some workplaces outside the hospitality, catering and leisure industries before the law's entry into force. However, this would probably have been rare in these industries; a delayed implementation beyond January 2006 is much more likely, because the law itself provided for an eight-month moratorium on the obligation to establish areas for smokers in many facilities affected by the ban. In any case, two facts virtually preclude attributing the 2005 mortality decrease to the law. First, the pre-law decreases also affected non-tobacco-related mortality, for which short-term changes in response to reductions in tobacco smoke exposure are not expected, and second, we did not identify more favourable changes in coronary/respiratory mortality among the target than the control groups when difference-in-differences regression models were performed for a hypothetical implementation date six months before the true date. However, the anti-smoking context in Spain during 2005 could have contributed to reinforcing the underlying downward trend in coronary/respiratory mortality during the pre-law period, diluting a possible subsequent favourable impact of the law, as indicated elsewhere (Seguret et al., 2014).

Comparison with other studies

The absence of a favourable impact on short-term mortality of the 2006 Spanish smoke-free law suggested by our study is not so surprising, given that the law allows wide exceptions in hospitality or recreational venues. This is compatible with the low post-law decreases in second-hand smoke exposure (measured with biological or airborne markers) in such venues found in previous Spanish studies (Fernandez et al., 2009; Lopez et al., 2012; Martinez-Sanchez et al., 2014; Nebot et al., 2009), and the lack of significant post-law changes in the prevalence of active smoking and other tobacco use indicators (Regidor et al., 2011; SEE, 2017). However, our results contrast with the favourable impact on coronary/respiratory morbimortality found in some previous Spanish studies (Aguero et al., 2013; Villalbi et al., 2009, 2011), which could be explained by inadequate control of important confounders such as the 2008 economic crisis (Aguero et al., 2013), and especially extreme temperatures and flu incidence (Aguero et al., 2013; Villalbi et al., 2009, 2011) or by geographic heterogeneity (Aguero et al., 2013; SEE, 2017; Villalbi et al., 2009). Thus, a study of hospital admissions found significant post-law decreases in circulatory/respiratory diseases in Barcelona, but not in Madrid (Galan et al., 2015), although the study did not include robustness checks. Elsewhere, certain benefits after partial smoking bans have been found (Frazer, Callinan et al., 2016; Tan & Glantz, 2012), although considerably smaller than after more comprehensive bans (Ferrante, Linetzky, Virgolini, Schoj, & Apelberg, 2012; Jones, Barnoya, Stranges, Losonczy, & Navas-Acien, 2014; Tan & Glantz, 2012; UDHHS, 2014; Ward, Currie, Kabir, & Clancy, 2013). However, in some areas the favourable impact of partial bans on tobacco smoke exposure or tobacco-related health problems has been minimal or non-existent (Fong et al., 2015; Seguret et al., 2014; Tabuchi, Hoshino, & Nakayama, 2016) or unclear (Christensen et al., 2014; Loomis & Juster, 2012; Sato et al., 2016). We also cannot rule out that studies showing a lack of favourable impact are less likely to be published -publication bias- (Lee et al., 2014; Meyers et al., 2009), or that in many studies the expected benefits of smoke-free laws in coronary mortality are overestimated due to inadequate confounding adjustment (Gasparrini et al., 2009).

Strengths and limitations

This study has many strengths. The results are generalizable throughout Spain because, although there were probably differences in law compliance between regions (SEE, 2017), the results barely changed when all the Spanish regions -18-, including 5 regions for which no air pollution indicators were available, were included in a sensitivity analysis. Since this was a cohort study in which the same participants are followed over time with few follow-up losses, it can be assumed that time invariant individual-level characteristics -observed and unobserved- remained constant throughout the periods, avoiding selection bias in prelaw-postlaw comparisons as well as numerator-denominator bias. Cohort aging would not introduce bias because age was entered as time-varying. Robustness checks were performed to examine validity of the results. The results did not change appreciably in the sensitivity analyses when a quadratic term for the underlying trend was used or when the heat- and cold-wave days were replaced by the ventile distributions of maximum and minimum temperature. Likewise, the results hardly changed when circulatory/respiratory ill-defined conditions -R00-R09- were removed from the non-tobacco-related outcome. Setting the follow-up end-point in December 2007 avoids the possible confounding of the effect of the Great Recession. However, there are limitations. A true control group without smoking ban implementation was not available, nor were individual indicators of health problems, tobacco smoke exposure or other risk behaviours. The adjustment for ecological covariates was imperfect, mainly because the region of residence was determined only at baseline. Time-varying unmeasured confounders could have influenced some results, although adjustment for the underlying time trend might have mitigated the possible confounding (Seguret et al., 2014). Thus, changes in tobacco prices could slightly attenuate a supposed favourable impact of the law because the annual increase was lower in the post-law -4.1%- than pre-law -6.1%- period, while the increase in the general price index was similar (INE, 2018). Relevant pre- and post-law population changes in other factors susceptible to influence circulatory/respiratory mortality such as hypertension, diabetes, hypercholesterolemia, obesity or management of coronary disease have not been identified (Villalbi et al., 2011). Compliance with the law was generally high in workplaces -including retail stores and other closed public places-, and somewhat lower in hospitality and recreational venues, which would not explain their absence of favourable effect (SEE, 2017; Villalbi, 2009).

Implications for policy and practice

Smoke-free laws probably have a very favourable impact on long-term population morbimortality through the reduction of smoking behaviour and exposure to second-hand tobacco smoke. Unfortunately, quantification of their impact would require expensive follow-up studies, adjusting for multiple factors. In contrast, there is clear evidence of benefits on short-term population morbimortality of comprehensive laws banning smoking in all indoor public spaces without exceptions (Jones et al., 2014; Tan & Glantz, 2012; Ward et al., 2013). Partial smoke-free laws may also be relevant public health interventions, although their favourable effect on short-term morbimortality may be small or unclear, especially when they include broad exceptions as did the 2006 Spanish law.

The inclusion of suitable control groups without intervention in study designs is highly recommended to improve confounding control. However, this is often difficult or impossible in the real world, so single-group ITS designs are often used. As this study shows, these designs are very prone to threats to their internal validity (such as the effect of confounders that act close in time to the intervention). Consequently, routine robustness checks should be systematically introduced, especially when tobacco-related morbimortality outcomes are used, since they represent the end of the causal chains and can be influenced by multiple confounding factors (Gasparrini et al., 2009; Linden, 2017). With these robustness checks, the single-group ITS design becomes a quasi-experimental design with medium strength, which is very useful for assessing public health interventions in real-world settings, since it is often inexpensive and highly feasible. However, if these checks are lacking, there is a considerable risk of drawing hasty and inadequate conclusions about the existence or magnitude of the impact.

Contributorship statement

Gregorio Barrio (GB) and Enrique Regidor (ER) conceived the article, coordinated the design of the study, and writing the article; María José Belza and Elena Ronda carried out the bibliographic searches and obtained and prepared the data on ecological variables, Rocío Carmona and Juan Hoyos carried out the statistical analysis and reviewed the consistency of data included in the paper; GB and ER wrote the first draft and the final version of the manuscript; all authors made substantial contributions to the interpretation of the results, critically reviewed them, approved the version of the manuscript submitted for publication and agreed to take public responsibility for all aspects of the work, assuring that questions related to the accuracy or integrity of any part of the work has been appropriately investigated and resolved.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugpo.2019.07.018.

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